

REMARKS

Upon entry of the present amendment, claims 1-8 will remain pending in the above-identified application and stand ready for further action on the merits.

Newly added claims 7 and 8 find support in the original application, including original claims 5-6. In this respect, claims 7 and 8 are identical to claims 5 and 6, but depend from claim 2.

Claim Rejections Under 35 USC § 102 & § 103

Claims 1-6 have been rejected under 35 USC § 102(b) as being anticipated by Fujioka et al. (US 5,011,692). Further, claims 1-6 have been rejected under 35 USC § 103(a) as being unpatentable over Sano et al. (EP 0659406) in view of Fujioka et al. Reconsideration and withdrawal of each of these rejections is requested based on the following considerations.

The Present Invention and Its Advantages

The present invention provides for controlled release preparations having multi-layer structures. The preparations more particularly relate to controlled drug-release formulations having multi-layer structures, wherein one or more drugs can separately be released with a different behavior *in vivo*, for the purpose of exhibiting effectively the efficacy thereof.

In the present specification, experiments are carried out and reported between preparations of the present invention and comparative preparations. As seen upon reviewing Experiments 1-4 at pages 20-21 of the specification and Figures 2-5 referred to therein, the Examiner can easily see that the compositions of the present invention possess advantageous properties, and allow one to easily release one or more drugs separately with different behaviors *in vivo*.

Distinctions Over Fujioka

As pointed out by the Examiner, Fujioka discloses a formulation which comprises one layer (A) and second layer (B) and which can be in the shape of a cylinder. However, the formulation of Fujioka differs from that of the present invention because "the outer and inner layers are concentrically located in diametral direction" in the instant invention (see claim 1 of the present application) but not according to the teachings of Fujioka.

Thus, while Fujioka discloses "a pharmaceutical preparation which comprises" layers A and layers B "disposed alternately" (see Fujioka, column 2, lines 31-36), it does not disclose an element of the present invention where the outer and inner layers are "concentrically located in diametral direction". In addition, a formulation of Fujioka has "the whole surface extending in the direction perpendicular to the layer plane being coated" (see

Fujioka, column 2, lines 36-38). That is, both layers A and B to be exposed on the surface of both ends of Fujioka's formulation are coated. Such ends correspond to the ends in axial direction of the formulations of the present invention at which inner and outer layers are exposed. Accordingly, Fujioka's formulation differs from that of the present invention because the former does not satisfy an element of the latter that "both or one ends in axial direction are open".

Further, even if Fujioka may disclose in Examples 1 and 2 a cylindrical formulation having an end that is open, said formulations are prepared by compression-molding of several components on a tableting machine to form a laminated cylindrical pellet, which is then coated with a silicone polymer except for one release face (layer) (column 7, lines 41-62, column 8, lines 24-39). Thus, such formulations are ones wherein 2 kinds of thin cylindrical layers are alternately layered, and wherein the surface thereof except for that at one end is coated with a polymer. Accordingly, in such formulation disclosed in the examples of Fujioka, each layer is alternately layered in the axial direction of the cylindrical pellet and are not "concentrically located in the diametral direction" like a formulation of the present invention. Accordingly, Fujioka's formulations as disclosed in Examples 1 and 2 thereof are quite distinct and different from a formulation of the present invention.

In addition, because layer A containing a drug of Fujioka's formulation is "degradable in living organism" (see column 2, line 60), such a formulation differs from a formulation of the present invention, wherein a "water-soluble drug,...,is dispersed in a carrier comprising a biologically non-degradable hydrophobic material".

Based upon the above considerations, it is clear that the cited Fujioka et al. reference does not teach each of the elements recited in the pending claims, and therefore it can not serve as a proper basis for rejecting Applicants' claims under 35 USC § 102(b).

Distinctions Over Sano in view of Fujioka

Sano does not disclose that its formulation can contain a drug in its outer layer. To the contrary however, a formulation of the present invention comprises "an outer layer wherein a water soluble drug is dispersed" (see claim 1). Thus, the formulation of the present invention differs from Sano's formulation in the dispersing of a drug in the outer layer. In Fujioka's formulation, "the whole surface extending in the direction perpendicular to the layer plane being coated with a polymeric material" (see Fujioka, column 2, lines 36-38, "polymeric material C") which would correspond to the outer layer of a formulation of the present invention. As such, Fujioka fails to disclose that a drug can be contained in the

polymeric material C, and therefore, those skilled in the art would not be motivated to arrive at a formulation of the present invention based upon a consideration of the disclosure of Fujioka.

More particularly, it is submitted that those skilled in the art would not arrive at a formulation of the present invention containing a drug in the outer layer by considering Sano's formulation in combination with Fujioka's formulation, since neither of these references' formulations contain a drug in the outer layer.

In addition, when taking note of a drug-containing layer, Fujioka's formulation is one wherein each layer is layered in a diametral direction but wherein such layers are not concentrically located in a diametral direction, which is unlike the formulations of the present invention (see instant claim 1). Therefore, there is no motivation for those skilled in the art, to combine Sano's formulation with Fujioka's formulation in a fashion that would arrive at the instant invention as claimed. Further, as the structure of Fujioka's formulation is so different from that of Sano's formulation, combining them is virtually impossible, and at the least requires that one disregard what the references themselves explicitly teach.

Because of the differences in such elements between the cited references and the instant claims, the formulations of the present invention "can release two or more drugs separately at appropriate

rates depending on disease or a preparation where the release behaviors of one or more drug can be precisely controlled" (see the present specification, page 3, lines 18-21).

Sano's formulation, however, "releases a water-soluble drug intracorporeally over prolonged periods of time at a nearly constant rate (zero-order release)" (Sano, page 3, lines 53-55), the effects of which clearly differ from those of a formulation of the present invention. In addition, Fujioka's formulation provides "sustained pulse-wise release" of a drug (Fujioka, column 2, lines 31-32), which effects are also quite different from those obtained with a formulation of the present invention. Therefore, there is no motivation for those skilled in the art, to combine Sano's formulation with Fujioka's formulation in any manner that would arrive at the instant invention as claimed. Any rejection based on the disclosures of such references is by necessity simply based on a "hindsight reconstruction" theory of obviousness, which is unacceptable and contrary to the statute itself.

Accordingly, it is clear that even upon considering the disclosures of Sano and Fujioka in combination, or separately, the same are completely incapable of either anticipating or rendering obvious Applicants' claimed invention.

CONCLUSION

Based upon the amendments and remarks presented herein, the Examiner is respectfully requested to issue a Notice of Allowance, clearly indicating that each of the pending claims 1-8 are allowable at present.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey (Reg. No. 32,881) at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Attached hereto is a marked-up version of the changes made to the application by this Amendment.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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By 

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JWB/end
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Attachment: Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 7-8 have been added.